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| EXAMINER |
|---|
| O'DELL, DAVID K |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/540,336 | TIMMERS ET AL. | |
| | Examiner | Art Unit | |
| | David K. O'Dell | 1625 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,4-13 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-13, 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1, 4-13, 16 are pending in the current application.

2. This application is a national stage of PCT/EP03/51025 filed November 16, 2003 which claims priority to U. S. Provisional Application 60/435,040 filed December 20, 2002 and European Union Application (EPO) 2102866.7, filed December 20, 2002.

### *Response to Arguments*

3. Applicant's arguments filed November 13, 2007 have been fully considered but they are not persuasive. The rejections under 35 U.S.C. 102 (e) are withdrawn in light of the claim amendment. In light of the claim amendments a provisional 103(a) rejection is made. The rejections for enablement are maintained as the directions for the preparation and function of all the scope of "heteroaryl" moiety is not enabled. The number of examples provided by the specification are few and have been discussed previously (and are reproduced here again). It would appear that the applicant is arguing that essentially any molecule, even molecules of unknown structure, can be made without undue experimentation. This is in fact not the situation in the chemical arts. As stated in a recent book on the subject:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise

undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work……Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) [preface].....even structurally simple compounds often turn out not to be so easy to make as initially thought. [pg. 2]..... As illustrated by the examples discussed below, a good retrosynthesis requires much synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures [pg. 3]..... As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural features of a given starting material, and unexpected products may readily be formed. [8].....Even the most experienced chemist will not be able to foresee all potential pitfalls of a synthesis, specially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even simple chemical transformations can no longer be performed. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity [pg. 9]....." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface pg. 1-15. **(E)**

The examiner (*vide infra* and in the previous action ) serve to show the scope that is enabled by the specification, in terms of the compounds (at least synthetically), and the teaching of the prior art. . A recent ruling by the Federal circuit discusses enablement in the context of the automotive art, but there is little difference in the position of the court and the position of the examiner instant case, ATI v. BMW et. al. (Fed. Cir. 2007):

> "We also reject ATI's argument that because the specification enables one mode of practicing the invention, viz., mechanical side impact sensors, the enablement requirement is satisfied. We addressed and rejected a similar argument made in Liebel-Flarsheim Co. v. Medrad, Inc., 481 F.3d 1371 (Fed. Cir. 2007). In that case, the invention was a front-loading fluid injector system with a replaceable syringe capable of at 1373. We construed the asserted claims, as urged by the patentee, to include an injector with and without a pressure jacket. Although the specification clearly enabled an injector with a pressure jacket, we concluded that it did not enable an injector without such a jacket and that the claims were invalid for lack of enablement. at 1379. We stated that there "must be 'reasonable enablement of the scope of the range' which, in this case, includes both injector systems with and without a pressure jacket." withstanding high pressure for delivering a contrast agent to a patient. Id. Id. Id. at 1380 (internal citation omitted).
>
> Similarly, in this case, the claim construction of the relevant claim limitation resulted in the scope of the claims including both mechanical and electronic side impact sensors. Disclosure of only mechanical side impact sensors does not permit one skilled in the art to make and use the invention as broadly as it was claimed, which includes electronic side impact sensors. Electronic side impact sensors are not just another known species of a genus consisting of sensors, but are a distinctly different sensor compared with the well-enabled mechanical side impact sensor that is fully discussed in the specification. Thus, in order to fulfill the enablement requirement, the specification must enable the full scope of the claims that includes both electronic and mechanical side impact sensors, which the specification fails to do. We stated in Liebel: "The irony of this situation is that Liebel successfully pressed to have its claims include a jacketless system, but, having won that battle, it then had to show that such a claim was fully enabled, a challenge it could not meet." Id. at 1380. ATI sought to have the scope of the claims of the '253 patent include both mechanical and electronic side impact sensors. It succeeded, but then was unable to demonstrate that the claim was fully enabled. Claims must be enabled to correspond to their scope."

The disclosure of a few examples of "heteroaryl" does not enable all "heteroaryl" or "heterocyclic" on R6 and R5 (which is nested to R7, which is in turn nested to R8 and R9). A narrowing of the claim language on "heterocycloalkyl" and "heteroaryl" would obviate the rejection.

The rejection of the method claim 16 for lack of enablement with respect to the "methods of fertility regulation" is not enabled for the reasons of record. The applicant has apparently misconstrued the examiner's statement regarding the activity of the compounds. No activity for the compounds is given, however under the scope given a single compound would need to do two opposite things at a receptor. The statement on pg. 7 of the remarks:

> "Applicants submit that some of the claimed compounds, as indicated in the specification, indeed show both agonist and antagonist activity in the assays described in example 51 of the specification. Applicants thus submit that some compounds can interact with the FSH-receptor and have both agonist and antagonist activity. The Examiner has provided no evidence to question this experimental evidence..."

Pg. 51 of the specification is reproduced below:

> **Compounds of all examples exhibited an $EC_{50}$ ($IC_{50}$) value of less than $10^{-5}$ M in either an agonistic or antagonistic assay set-up or both. The compounds of examples 5-8, 10-14, 16, 18-20, 33-35, 37, 38, 41 and 45-50 showed an $EC_{50}$ of less than $10^{-7}$ M in at least one of the assays.**

It is clear that no data is present. While some of the claimed compounds may be full agonists or antagonists, a single compound cannot be both a full agonist and an antagonist at the same time (or concentration), yet this is what is being alleged. The activation of the receptor through Gs linked pathway in the presence or absence of a known ligand is being measured in the assay. Based on the teaching of van Straten in The Journal of Medicinal Chemistry 2005, 48, 1697-1700, these compounds appear to be antagonists, which is at odds with the specification. The specification states they all have EC50's of less than 100nM in at least one of the assays. It would appear that more than one assay of agonism is being reported here, however only one assay is described. Where are the other assays? The physiological outcome on fertility of an

antagonist vs. an agonist is radically different. The paucity of data in the specification, the relatively poorly developed understanding of the effect of FSH receptor agonists/antagonists, and the myriad of different physiological functions encompassed by the term "fertility regulation" clearly warrant the conclusion of lack of enablement which was supported by references testifying to the state of the art. This action is made **FINAL**.

## *Claim Rejections – 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 4-13 are rejected under 35 U.S.C. 103(a) as being obvious over Van Straten, et. al. PCT Int. Application WO 20030004028, filed June 25, 2002 or Van Straten, et. al. U.S. Pre-Grant Publication 2004/0236109. (cited previously). The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or

declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

**Determination of the scope and content of the prior art**

***(MPEP 2141.01)***

Van Straten et. al. teaches numerous compounds of the instant case that amount to change of the position of substituents, or other minor variations available within the general teeaching.

***Ascertainment of the difference between the prior art and the claims***

***(MPEP 2141.02)***

Van Straten et. al. evidently do not expressly teach the compounds of the instant case, based on a proviso, but the general teaching provides the compounds of the instant case that are only minor variations.

**Finding of prima facie obviousness**

***Rational and Motivation***
***(MPEP 2142-2143)***

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare the compounds of the instant case. The compounds of the claims at hand are analogs of old compounds. One of ordinary skill would be motivated to make the compounds of the invention because he would expect the compounds to have similar properties, indeed we see that these compounds have the same properties. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its **analogs** or isomers, either geometric isomers (*cis* v. *trans*) or position isomers (emphasis added) (*e.g. ortho v. para*)".

***Double Patenting***

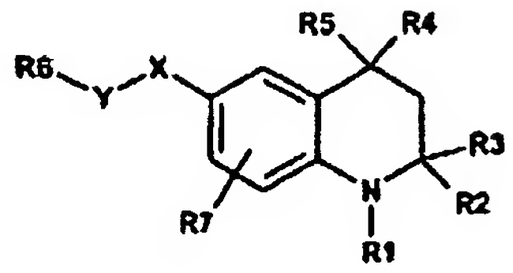
The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined

application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1, 4-13, 16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of copending Application No. 10/482,707. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims overlap in scope substantially and cover the same compounds. The wording is only slightly different and the '707 application is broader but where X is NH and Y is CO the compounds of the instant case are produced. It is noted that some of the same species are present in both applications (see 102(e) rejection).



Formula I

or a pharmaceutically acceptable salt thereof, wherein

$R^1$ is formyl, (1-6C)alkylcarbonyl or (1-6C)alkylsulfonyl;

$R^2$ and $R^3$ are H or (1-4C)alkyl;

$R^4$ is phenyl, optionally substituted with one or more substituents selected from the group hydroxy, amino, halogen, nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)(di)alkylamino.

$R^5$ is (1-4C)alkyl;

Y-X is C(O)-O, $S(O)_2$-O, NHC(O)-O, NHC(S)-O, OC(O)-O, bond-O, C(O)-NH, $S(O)_2$-NH, NHC(O)-NH, NHC(S)-NH, OC(O)-NH, bond-NH, NH-C(O), O-C(O), NH-$S(O)_2$, or O-$S(O)_2$ or X-Y is a bond;

$R^6$ is H, except for Y-X is a bond, trifluoromethyl, (1-6C)alkyl, 1- or 2-adamantyl(1-4C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-9C)heteroaryl, (3-6C)cycloalkyl, (2-6C)heterocycloalkyl, (1-4C)alkylthio(1-4C)alkyl, (6-10C)aryl(1-4C)alkyl, (3-9C)heteroaryl(1-4C)alkyl, (3-6C)cycloalkyl(1-4C)alkyl, (2-6C)heterocycloalkyl(1-4C)alkyl, $R^8$,$R^9$-aminocarbonyl(1-4C)alkyl, $R^8$,$R^9$-amino(1-4C)alkyl, $R^8$-oxycarbonyl(1-4C)alkyl, $R^8$-oxy(1-4C)alkyl, $R^8$-carbonyl(1-4C)alkyl or (6-10C)aryl, whereas if (6-10C)aryl is phenyl, phenyl may be optionally substituted with hydroxy, amino, halogen, nitro, trifluoromethyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)(di)alkylamino, (6-10C)aryl, (6-10C)aryloxy, (6-10C)aryl(1-4C)alkoxy, (3-9C)heteroaryl, (3-9C)heteroaryloxy, (3-9C)heteroaryl(1-4C)alkoxy, (1-4C)alkylcarbonylamino, (1-4C)alkylcarbonyloxy, (3-6C)cycloalkylcarbonyloxy,

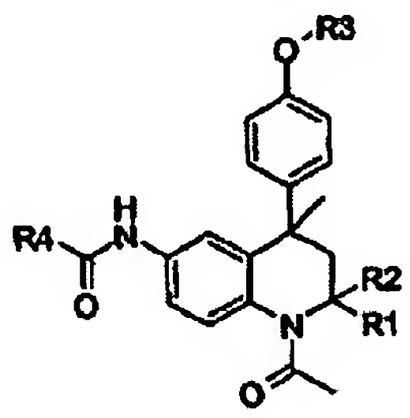
This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. The applications appear to have a common assignee.

6. Claims 1, 4-13, 16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of copending Application No.

10/540,335. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims overlap in scope substantially and cover the same compounds. The wording is only slightly different and the '335 application is narrower but the genus produced is nearly identical. It is noted that some of the same species are present in both applications.

**Claims**

**1. A tetrahydroquinoline derivative according to Formula I,**




**Formula I**

**or a pharmaceutically acceptable salt thereof, wherein**

**$R^1$ and $R^2$ are H, Me;**

**$R^3$ is (2-6C)heterocycloalkyl(1-4C)alkyl, (2-5C)heteroaryl(1-4C)alkyl, (6C)aryl(1-4C)alkyl, (1-4C)(di)alkylaminocarbonylamino(2-4C)alkyl, (2-6C)heterocycloalkylcarbonylamino(2-4C)alkyl, $R^5$-(2-4C)alkyl or $R^5$-carbonyl(1-4C)alkyl;**

**$R^4$ is (2-5C)heteroaryl, (6C)aryl, (3-8C)cycloalkyl, (2-6C)heterocycloalkyl or (1-6C)alkyl**

**$R^5$ is (di)(1-4C)alkylamino, (1-4C)alkoxy, amino, hydroxy, (6C)arylamino, (di)(3-4C)alkenylamino, (2-5C)heteroaryl(1-4C)alkylamino, (6C)aryl(1-4C)alkylamino, (di)[(1-4C)alkoxy(2-4C)alkyl]amino, (di)[(1-4C)alkylamino(2-4C)alkyl]amino, (di)[amino(2-4C)alkyl]amino or (di)[hydroxy(2-4C)alkyl]amino.**

1.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. The applications appear to have a common assignee.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 4-13, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds, does not reasonably provide enablement for the protracted list of compounds bearing the protracted list of substituents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

***(A) The breadth of the claims;***
***(B) The nature of the invention;***
***(C) The state of the prior art;***
***(D) The level of one of ordinary skill;***
***(E) The level of predictability in the art;***
***(F) The amount of direction provided by the inventor;***
***(G) The existence of working examples; and***
**(H) The quantity of experimentation needed to make or use the invention**

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

**(A) The breadth of the claims:** The claims are very broad encompassing a variety of heterocycles (mainly on R4 and R5), bearing multiple substitutions **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic chemist. **(C) The state of the prior art:** Little prior art exists on these complex compounds, however the synthesis will be

evaluated on what is known using scientific principles. **(E) The level of predictability in the art:** Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3. **(F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** The examiner will first consider the Markush structure I of claim 1, and the inherent limitations of the chemistry used to prepare the examples as well as starting materials and then address the influence of these groups on the utility.

As per MPEP:

> A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

While a vast array of anilines are commercially available for the Skraup reaction. The substituents R4 and R5 apparently have enormous permutations due to their apparent identity as R7 which is actually a list of 10 groups which then further contain the groups R8 and R9 which are themselves more than six groups. Where can one purchase or prepare the required anilines possessing these groups? While apparently a Lewis acid catalyzed version of the Skraup

reaction is used to construct the quinoline nucleus, the Skraup has been shown to be sensitive to substituents on the starting aniline (The Chemistry of Heterocyclic compounds: Quinolines PART 1, Jones, Gurnos editor Wiley: New York, 1977 pg. 104-117. ) For example the claims are drawn towards "carbonyloxy" groups which are esters and these groups are "susceptible to decarboxylation" a "further disadvantage" (Jones, ibid. pg. 104 at b.). "Other groups that are modified or eliminated during a Skraup synthesis are the sulphonic acid group, and ether or ester groups." *p*-acetylaniline also fails to undergo the reaction (Jones ibid. pg. 105). One very serious problem is the formation of regioisomeric 5 and 7 quinolines when using meta-substituted anilines, which may or may not be separable.

While some of these limitations are clearly synthetic, perhaps more importantly are the requirements for activity at the FSH receptor. The only information as to what these compounds are doing in the pharmacological sense is the following statement: "Compounds of all examples exhibited an EC50s (IC50s0) value of less than $10^{-5}$ M in either an agonistic or antagonistic assay set-up or both." A single compound cannot perform as both a full agonist and as an antagonist. Indeed we see that a switch from aganoist to antagonist activity occurs with 4-Cl phenyl (Nicole C. R. van Straten, Twan H. J. van Berkel, Dennis R. Demont, Willem-Jan F. Karstens, Remco Merkx, Julia Oosterom,Ju¨ rgen Schulz, Richard G. van Someren, Cornelis M. Timmers, and Peter M. van Zandvoort "Identification of Substituted 6-Amino-4-phenyltetrahydroquinoline Derivatives: Potent Antagonists for the Follicle-Stimulating Hormone Receptor" Journal of Medicinal Chemistry **2005**, *48*, 1697-1700.) "Aromatic susbstituents in position 6 [$R_6$ of the instant claims] are preferred…" van Straten ibid. pg. 1698. There is an apparent size constraint

on substituents, "space is limited because introduction of an extra t-butyl group in **11** led to a drop in potency" van Straten ibid. pg. 1698.

The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification , at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has few working examples in this unpredictable art without undue experimentation.

8. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to "methods of fertility regulation", however no clear nexus exists between the compounds described here and "methods of fertility regulation". In the words of van Straten et. al. (ibid. pg. 1700 conclusion) these compounds "may serve as starting points for further optimization to evaluate the feasibility of FSH receptor antagonists as a novel method for contraception."

The effect physiologically of a compound that binds and perturbs the FSH-R (a GPCR) is unclear. While knockout mice are clearly sterile ("Genetic elimination of the alpha subunit in mice by homologous recombination (7) causes complete deficiency of all three glycoprotein hormones, and animals of both sexes are not only sterile but also hypothyroid." M. Ram Sairam and Hanumanthappa Krishnamurthy "The Role of Follicle-Stimulating Hormone in

Spermatogenesis: Lessons from Knockout Animal Models" Archives of Medical Research 32 (2001) 601–608. ) Mutants which presumably have some receptor function (as in the instant case) "exhibit delayed sexual maturity and reduced fertility". The real problem here is that this receptor is a GPCR with a vast number of binding sites and conformations each of which may be associated with a distinct physiological outcome. One reviewer has summarized the situation this way (Terry Kenakin and Ongun Onaran "The ligand paradox between affinity and efficacy: can you be there and not make a difference?" *TRENDS in Pharmacological Sciences* **2002**, *23*, 275-280):

"A probabilistic model of protein conformation can be used to quantify the probability of various receptor conformations and the effect of ligand binding on those conformations. The basic idea behind the probabilistic model is that the function of a receptor protein is not assigned to particular conformations of the receptor. Instead, the function arises as a result of ligand-induced perturbation of the distribution of conformational states over the conformational space of the receptor.....**The foregoing discussion leads to the general conclusion that if a ligand binds to the receptor, it most probably will produce a bias in the conformations of the receptor ensemble** [i.e. it will change the receptor by its presence (Fig. 3)]. Therefore, this suggests that all ligands with macro-affinity should be extensively studied for pharmacological activities other than simple G-protein activation because various physiological activities have been defined that are mediated by conformations not necessarily related only to G-protein activation..... Ligand activities that are not related to a standard G-protein-mediated physiological response **might have therapeutic utility**.

Here we have exactly this situation, namely a ligand with affinity, but no known function, which as Kenakin et. al. concluded "...the discovery of macro-affinity of a ligand for a receptor should be considered only a starting point for the optimal exploitation of a drug for therapeutic utility." One reviewer summarized the state of the art this way: Only in the clinic will the question of whether small molecule LHR and FSHR modulators will be successful as fertility-regulating agents be answered." (Guo, Tao "Small molecule agonists and antagonists for the LH and FSH receptors." Expert Opinion on Therapeutic Patents 2005 15(11) 1555-1564, conclusions.) There is no successful use of these compounds in an animal model and no clear correlation between antagonism of this receptor and a therapeutic outcome, thus undue experimentation would be required.

***Conclusion***

9. No claims are allowed. This action is FINAL. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Rita Desai can be reached on (571) 272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

RITA DESAI
PRIMARY EXAMINER

12/12/07